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TOPIC ARTICLE

Current concepts of polymicrogyria

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Abstract Polymicrogyria is one of the most common malformations of cortical development. It has been known for many years and its clinical and MRI manifestations are well described. Recent advances in imaging, however, have revealed that polymicrogyria has many different appearances on MR imaging, suggesting that is may be a more heterogeneous malformation than previously suspected. The clinical and imaging heterogeneity of polymicrogyria is explored in this review.

Keywords Polymicrogyria · Epilepsy · Malformations of cortical development · Magnetic resonance imaging

Introduction

Polymicrogyria is a malformation of cortical development in which the process of normal cerebral cortical development is disturbed late in the stage of neuronal migration or early in the stage of cortical organization; thus, it is considered a disorder of neuronal organization [1]. As a result of these disturbances to the developmental process, the deeper layers of the cerebral cortex develop abnormally and multiple small gyri form within the cortex [2]. Polymicrogyria has a range of histologic appearances, all having in common a derangement of the normal six-layered lamination of the cortex, an associated derangement of sulcation, and fusion of the molecular layer across sulci [3–5]. In areas of polymicrogyria, no normal sulci are seen. Causes of polymicrogyria include congenital infection (particularly cytomegalovirus infection [6, 7]), localized or diffuse in utero ischemia [8, 9], or mutations (Table 1) [10–23].

Patients with polymicrogyria may have a wide variety of clinical presentations, ranging from hemiparesis or partial epilepsy to developmental delay, quadriparesis, and medically refractory, intractable epilepsy; the neurologic disability appears to depend upon the portion[s] of brain involved, but may also depend upon the type of polymicrogyria and the presence or absence of associated anomalies. Neurologic manifestations are similar among patients who have polymicrogyria due to different causes [6, 22, 24, 25]. The severity of the clinical presentation and age at presentation depend mostly upon the extent of cortical involvement; bilateral involvement and involvement of more than half of a single hemisphere are poor prognostic indicators, portending moderate to severe developmental delay and significant motor dysfunction [25].

Polymicrogyria affects variable portions of the cerebral cortex: it may be focal, multifocal, or diffuse; it may be unilateral, bilateral, and asymmetrical; or bilateral and symmetrical. The most common location (in 60–70% of cases [26]) is around the sylvian fissure, particularly the posterior aspect of the fissure; however, any part of the cerebral cortex, including the frontal, occipital, and temporal lobes, can be affected [3, 24–28]. Polymicrogyria may be an isolated malformation or it may be associated with other brain malformations; when other malformations are identified, the most common are corpus callosum agenesis and hypogenesis, cerebellar hypoplasia [29], periventricular nodular heterotopia [30], and subcortical heterotopia [31]. Affected patients may be microcephalic, normocephalic, or macrocephalic [22].

Several specific syndromes are associated with cerebral polymicrogyria (Table 2). Some of the best known of these

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Table 1 Genes associated with polymicrogyria.

Gene	Location
SRPX2	Xq21.33-q23
RAB3GAP1	2q21.3
EOMES	3p21.3-p21.2
TUBB2B	6p25
KIAA1279	10q22.1
PAX6	11p13
COL18A1	21q22.3
Multiple genes	22q11.2

are Aicardi syndrome (OMIM 304050 [32, 33]), Delleman syndrome (oculo-cerebral-cutaneous syndrome, OMIM 164180 [34, 35]), DiGeorge syndrome (OMIM 188400, also called the 22q11.2 deletion syndrome in which several genes are deleted [19]), Warburg Micro syndrome (OMIM 600118 [36–38]), and D-bifunctional protein deficiency (OMIM 261515) [39]. Many others will likely be found.

The imaging appearance of polymicrogyria is variable. This variability is most likely a result of three factors: imaging factors (amount of gray matter–white matter contrast, thickness of the slices); the stage of maturity/myelination of the brain at the time of the imaging study; and, in all likelihood, the type of PMG. In a previous analysis of PMG, I noted that it can have a coarse appearance or a delicate appearance and that the appearance seen in the so-called cobblestone malformations differs from that seen in most bilateral polymicrogyria syndromes [40]. The precise reasons for these differing appearances are not known, but the development of the cerebral cortex is so complex that it is not surprising that disruptions of the processes of late cortical migration and cortical organization at

Table 2 Multiple congenital anomaly syndromes with polymicrogyria.

Syndrome	Anomalies	Gene
Aicardi syndrome	Callosal agenesis Polymicrogyria	Not known
	Heterotopia [periventricular and subcortical]	
	Retinal anomalies	
Delleman syndrome	Callosal agenesis Cystic microphthalmia	Not known
	Frontal polymicrogyria	
	Periventricular heterotopia	
	Large, dysplastic tectum	
	Absent Cb vermis	
DiGeorge syndrome	Parathyroid hypoplasia Thymic hypoplasia	22q11.2
	Cleft palate	
	Cardiac malformations	
	Facial anomalies	
	Polymicrogyria [perisylvian, right hemisphere preferred]	
Warburg Micro syndrome	Microcephaly Microcornea	2q21.3
	Congenital cataract	
	Optic atrophy	
	Hypogenitalism with hypotonia	
	Callosal hypo- or agenesis	
	Frontoparietal polymicrogyria	
D-bifunctional protein deficiency	Generalized osteopenia Bilateral perisylvian polymicrogyria	5q2
	Large anterior fontanelle	
	Frontal bossing	
	Up-slanting palpebral fissures	
	Hypertelorism	

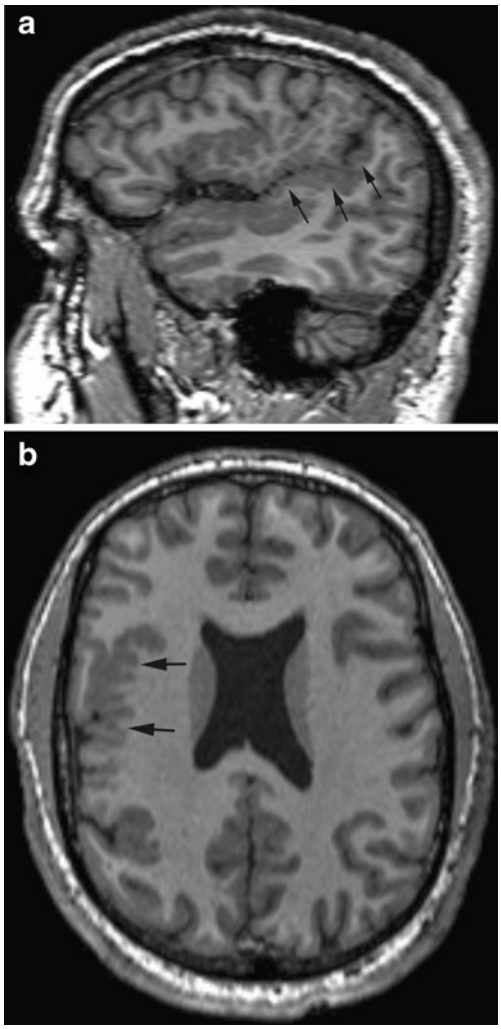

Fig. 1 Parasagittal (**a**) and axial (**b**) T1-weighted images show the delicate appearance of PMG (*black arrows*) in the right sylvian and suprasylvian cortex. Note the continuity of the posterior sylvian fissure on the parasagittal image (**a**); this is diagnostic of perisylvian PMG

different stages might result in slightly different malformations. The cortical surface can have multiple small, delicate gyri (Fig. 1) or appear thick and irregularly bumpy (Fig. 2) or be paradoxically smooth (Fig. 3) because the outer cortical (molecular) layer fuses over the microsulci. Sometimes the cortex appears thick and coarse (with an appearance of "palisades" of cortex [40], (Fig. 4)), while other times the microgyri appear fine and delicate (Fig. 1), even when the brains are similarly myelinated. However, these variations in appearance may not be detectable on routine, 5-mm thick images. Therefore, images with thin sections and optimal gray matter–white matter contrast [we acquire volume 3DFT spoiled gradient acquisition (T1 weighted) and volume 3DFT fast spin echo (T2 weighted) images, both in the sagittal plane with ≤1.5 mm partition size] should always be acquired. Evaluation in three planes is often necessary to detect irregularities of the gray matter–white matter junction, which are often the most convincing evidence of dysplastic brain (Fig. 3) [41]; this is most easily accomplished via volumetric acquisition with display in all three orthogonal

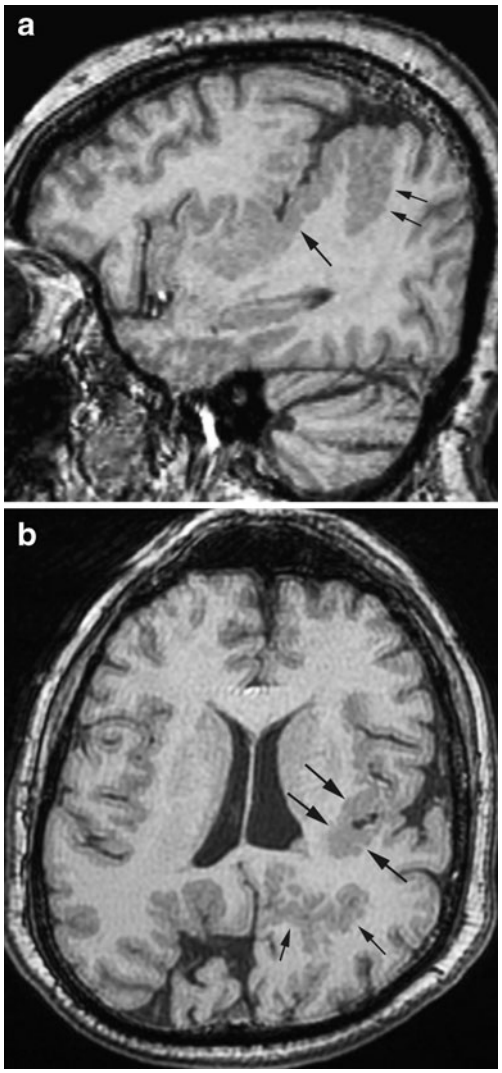

Fig. 2 Thick and irregularly bumpy, "coarse" appearance of PMG. Parasagittal (**a**) and axial (**b**) images show coarse PMG in the parieto-occipital (*small black arrows*) and perisylvian (*large black arrows*) regions

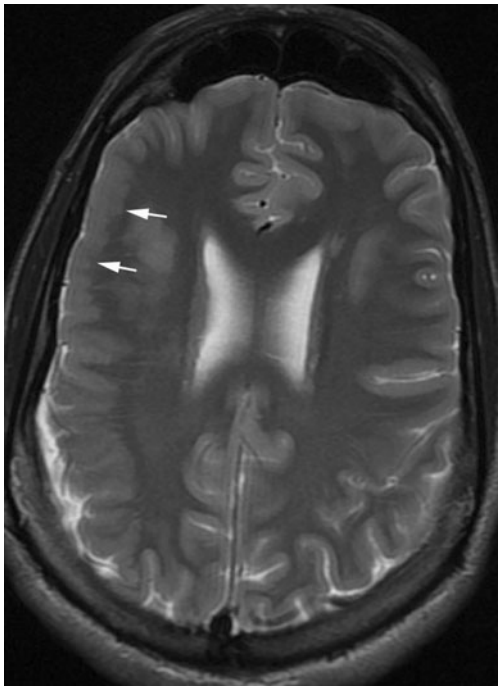

Fig. 3 Axial FSE T2 weighted image shows right frontal PMG (*white arrows*) with fusion of the molecular layer of cortex resulting in paradoxically smooth cortical surface

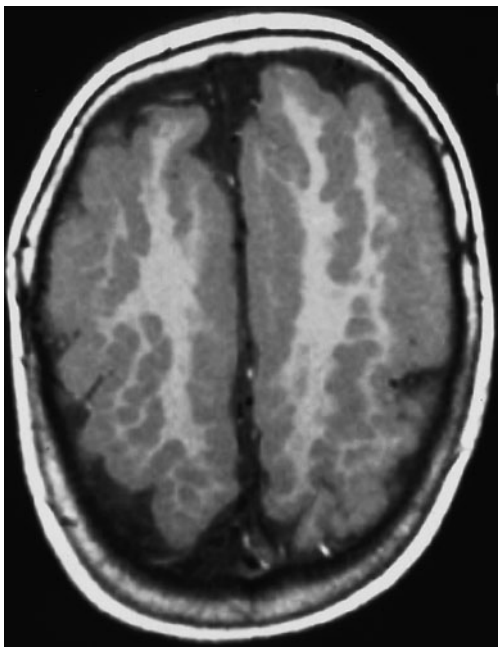

Fig. 4 Axial T1-weighted image shows diffuse coarse PMG with an appearance of "palisades" of cortex

planes (sagittal, axial, and coronal). The volume acquisitions can be displayed as three-dimensional surface images (Fig. 5) and can be utilized for stereotactic localization, aiding in surgical therapy, if appropriate. The degree of myelination affects the appearance. In unmyelinated regions, the inner surface of the polymicrogyric cortex looks thin [2–3 mm] and bumpy, while in myelinated areas it looks thicker (5–8 mm) and relatively smooth [42]. The reason proposed for this is that a 4–5 mm layer of gliotic white matter runs through the polymicrogyric cortex, blending in with white matter in the unmyelinated brain and blending in with cortex after myelination [42]. Finally, as stated earlier, polymicrogyria is almost certainly a heterogeneous malformation that can have many different appearances: thick and coarse, fine and delicate, with shallow or deep sulci. Whatever the reason, it is important to realize that a spectrum of cortical appearances, all having some sort of small gyri, can be seen in patients with polymicrogyria.

In addition to the variability of the appearance of polymicrogyria, the location of polymicrogyria is extremely variable. It may be superficial, with the cortex appearing flat and congruent to the arc of normal cortex, or may course radially inward, as if it were buckled or folded toward the ventricle. This infolding of cortex may be small or large, but close examination will show that the cortical features are similar [bumpy, irregular inner and outer cortical surfaces] in both the superficial and radially folded types. Polymicrogyria may be unilateral (~40%) or bilateral (~60%). The cortex surrounding the sylvian fissures is involved in ~80% of cases, with the frontal lobe being most commonly involved (~70%), followed by parietal (63%), temporal (38%), and occipital (7%) lobes [28]. The striate cortex, cingulate gyrus, hippocampus, and gyrus rectus are typically spared [28]. Polymicrogyria is sometimes calcified, but it is difficult to know the frequency because few patients are studied with CT. It is not clear if the calcification is of any significance. Finally, it is important

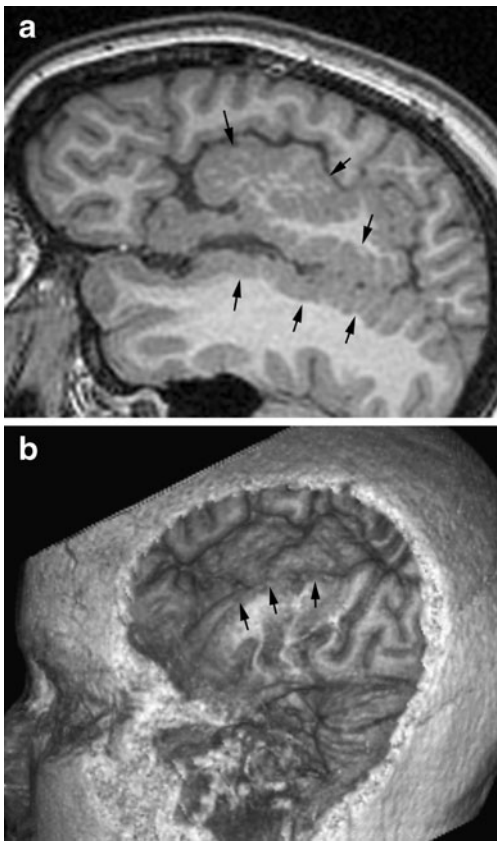

Fig. 5 Surface rendering of PMG from volumetric acquisition of data. **a** Image shows a parasagittal image of extensive perisylvian coarse PMG (*arrows*). The surface rendering (**b**) shows the absence of normal sulci and the bumpy cortical surface in the affected area (*arrows*)

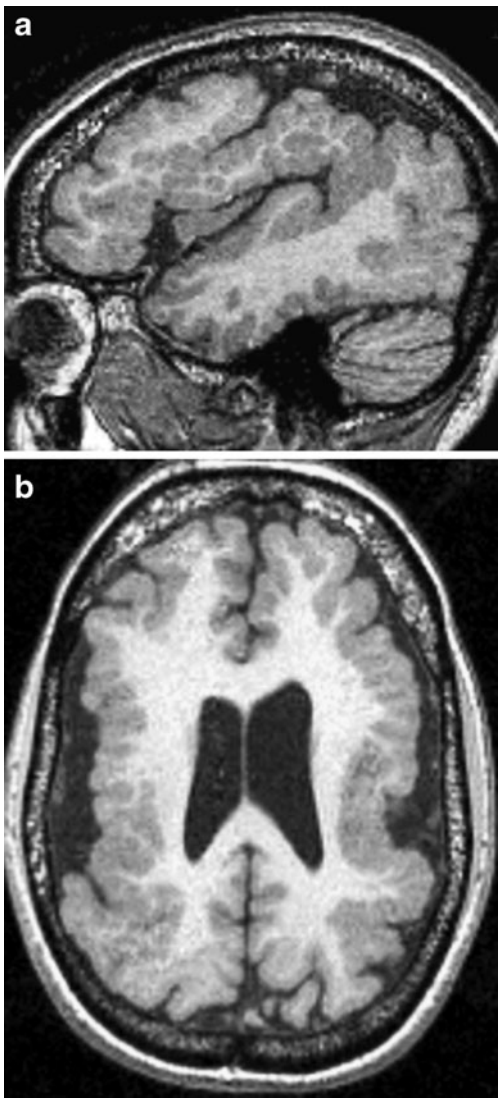

Fig. 6 Grade 1 perisylvian PMG. Parasagittal (**a**) and axial (**b**) T1-weighted images show coarse polymicrogyria extending from the frontal pole to the occipital pole

to recognize that anomalous venous drainage is common in areas of dysplastic cortex [43], seen in up to 51% of patients with polymicrogyria [28]. Large vessels are especially common in regions where there is a large infolding of thickened cortex. Such large vessels, when seen in association with abnormal, thickened cortex, should not be mistaken for vascular malformations. Angiography is not indicated.

Several syndromes of bilateral symmetrical polymicrogyria have been described; these should be recognized by neuroimagers. The best known and most common of these is bilateral perisylvian polymicrogyria (also called congenital bilateral perisylvian syndrome [44]). This syndrome may be sporadic or familial [15, 45]. The heterogeneous inheritance patterns suggest that mutations of several different genes can cause this malformation [45]; three locations (Xq21.33-q23 (*SRPX2*), 22q11.2, and Xq28) have been identified [13, 19, 20, 22]. Sporadic cases tend to present with more severe neurologic manifestations. A syndrome of developmental pseudobulbar palsy (oropharyngeal dysfunction and dysarthria, 100%), epilepsy (80–90%), mental retardation (50–80%), and, sometimes, congenital arthrogryposis has been described [44, 46–48]. Other patients are brought to attention in infancy or early childhood because of delayed development (60%), palatal dysfunction (40%), hypotonia (30%), arthrogryposis (30%), or motor deficits (25%) [47, 49]. Seizures are present in 40–60% and may be of many clinical types [47, 49]. Studies of familial cases of congenital bilateral perisylvian polymicrogyria show a lower incidence of these clinical manifestations [45, 50], possibly because patients with minimal symptoms are more readily identified and examined. A developmental reading disorder and reading impairment without severe motor or cognitive handicap may be the cause of seeking medical attention in this group [51]. Bilateral perisylvian polymicrogyria can be graded

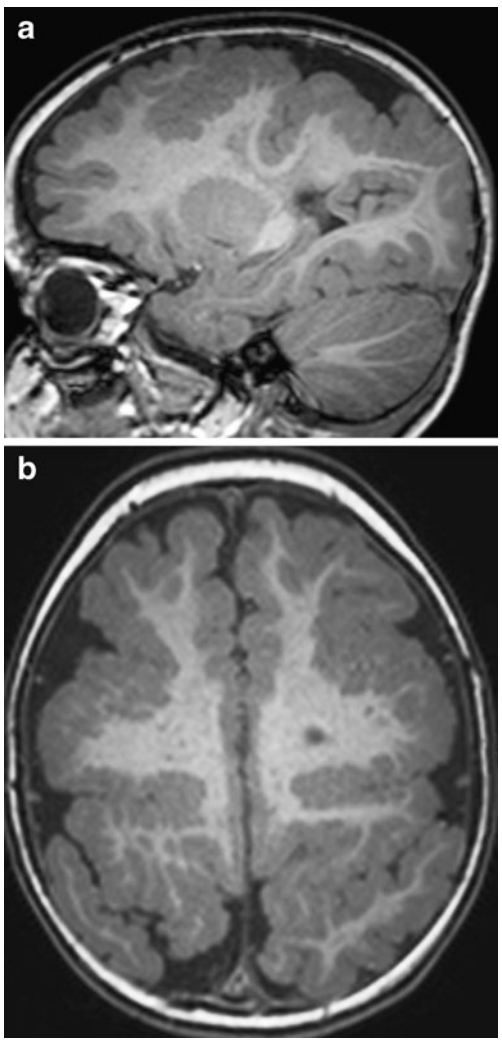

Fig. 7 Grade 2 perisylvian PMG. Parasagittal (**a**) and axial (**b**) images show coarse perisylvian polymicrogyria sparing the anterior frontal lobes and the occipital lobes

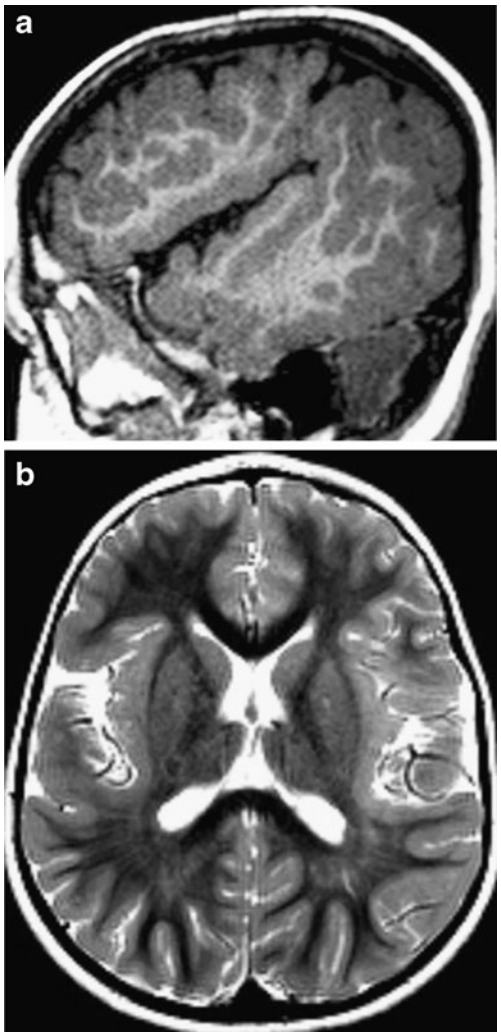

Fig. 8 Grade 3 perisylvian PMG. Parasagittal T1-weighted images (**a**) and axial T2-weighted images (**b**) show polymicrogyria limited to the insulae and operculae

according to severity on MRI (with grade 1 the most severe and grade 4 the mildest) [50]: Grade 1, with perisylvian polymicrogyria extending to the frontal or occipital pole (Fig. 6); Grade 2, with polymicrogyria extending beyond the perisylvian region but not to either pole (most common, Fig. 7); Grade 3, with polymicrogyria of the perisylvian region only (Fig. 8); and Grade 4, with polymicrogyria restricted to the posterior perisylvian regions.

Bilateral frontoparietal polymicrogyria is another well-defined syndrome [12, 52]. Affected patients are characterized by global developmental delay of at least moderate severity, seizures, disconjugate gaze, and bilateral pyramidal and cerebellar signs [52]. MR demonstrates symmetric

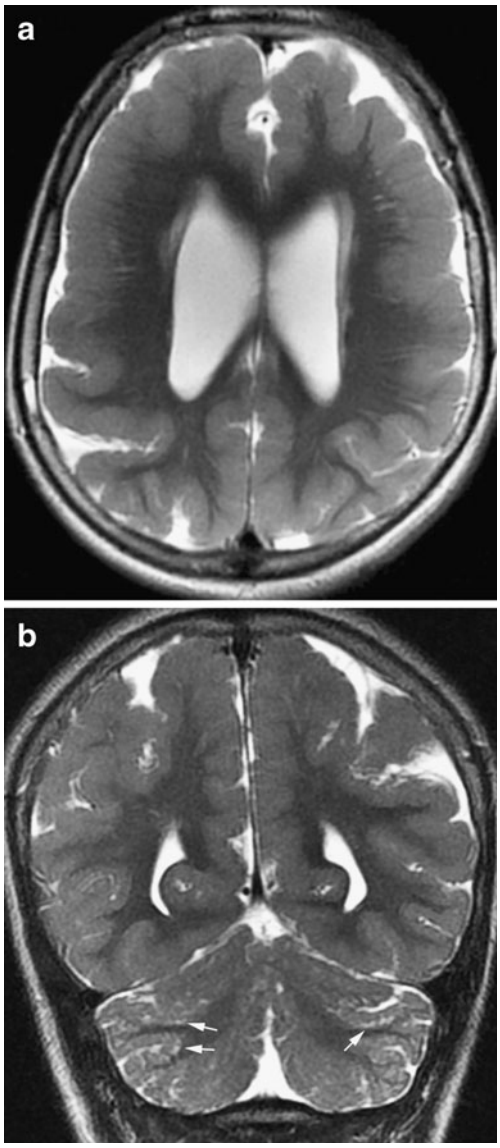

Fig. 9 Bilateral frontoparietal polymicrogyria. Axial (**a**) and coronal (**b**) T2-weighted images show a different appearance to the cortex, that of multiple radially oriented neuronal components separated by fibroglial stroma. Note the prominent cerebellar fissures and the subcortical cerebellar cysts (*arrows*)

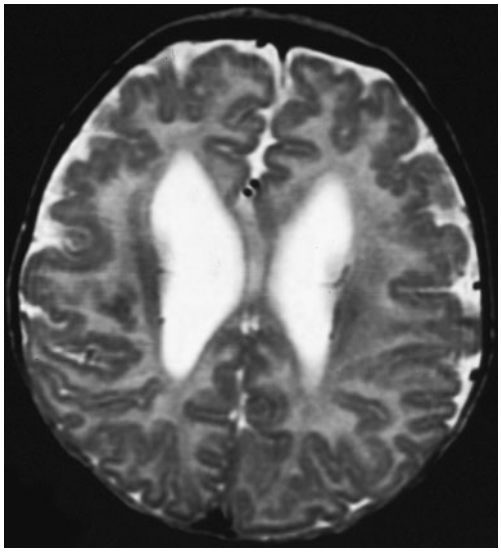

Fig. 10 Bilateral frontal polymicrogyria. Axial T2-weighted image shows delicate PMG in both frontal lobes. The lateral ventricles are somewhat dilated

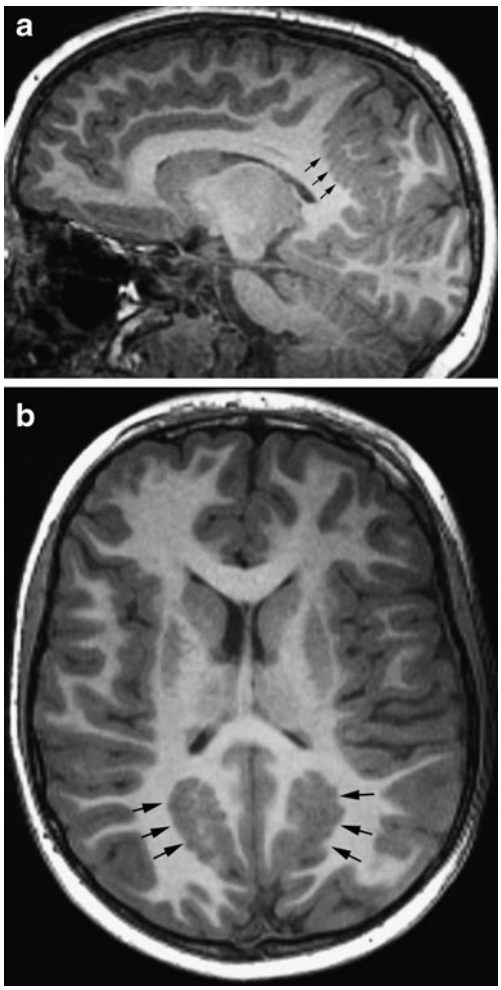

Fig. 11 Bilateral parasagittal parieto-occipital polymicrogyria. Parasagittal (**a**) and axial (**b**) T1-weighted images show coarse parasagittal infoldings (*arrows*) of polymicrogyria

cortical dysgenesis affecting the frontoparietal regions most severely, as well as ventriculomegaly, bilateral white matter signal changes, and small brainstem and cerebellar structures with dysmorphic cerebellar cortex (Fig. 9). The presence of the white matter changes and the posterior fossa anomalies is very uncommon for polymicrogyria syndromes. In addition, the cortical malformation itself has a slightly different appearance than that of most polymicrogyria. Indeed, the overall appearance of the brain is more similar to that of the so-called cobblestone malformations, associated with congenital muscular dystrophies and resulting from abnormalities of linkage of radial glial cells to the pial basement membrane overlying the developing cortex [53, 54]. Further research has shown that the pial basement membrane is regulated by *GPR56*, the gene that causes BFPP when mutated [55], and that mutations of *GPR56* cause gaps in the pial basement membrane and abnormal linkage of radial glial cells to that membrane [55]. Therefore, this disorder may fit better into the cobblestone malformations. Moreover, this observation raises the question of what precisely defines polymicrogyria and whether the different types of polymicrogyria should be analyzed and distinguished.

Other syndromes of bilateral symmetrical polymicrogyria have been described [56]. Several groups have described patients with spastic quadriparesis and epilepsy, on whom imaging shows bilateral symmetrical frontal polymicrogyria (Fig. 10) [57]. Guerrini et al. have described patients with bilateral medial parietal-occipital polymicrogyria (Fig. 11) [27, 58]. Other patients have combinations of the above-mentioned patterns (Fig. 2); thus, it appears that any region of cortex may be involved by bilateral, symmetrical polymicrogyria [56]. A syndrome of congenital hemiplegia and epilepsy has been described in patients with large areas of unilateral polymicrogyria [59]. These patients typically present in infancy with delayed motor development. A familial syndrome of unilateral polymicrogyria has also been described [60].

A syndrome of megalencephaly with polymicrogyria and hydrocephalus has been described. Affected children present at birth or in early infancy with macrocephaly and hypotonia; delayed motor and cognitive development become evident as they grow. Epilepsy, postaxial polydactyly, cutis marmorata, midface capillary malformation, and coarse facial features are frequently present [61–65]. Imaging reveals ventriculomegaly (from hydrocephalus) and polymicrogyria, which is most severe in the perisylvian region (typically Grade 1 or 2). This disorder is now thought to include those previously called megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome and macrocephaly capillary malformation syndromes [63–65].

In summary, polymicrogyria is not a single entity, but a group of disorders that has many causes and many clinical and radiological phenotypes. Imaging characteristics may be useful in helping to differentiate the different types of polymicrogyria, which may appear as one component of multiple congenital anomaly syndromes or as isolated CNS malformation. It is important for neuroimagers to acquire high-quality images in affected patients and carefully analyze the images to help to optimize the diagnosis and treatment.

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Conflict of interest statement I declare that I have no conflict of interest.

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